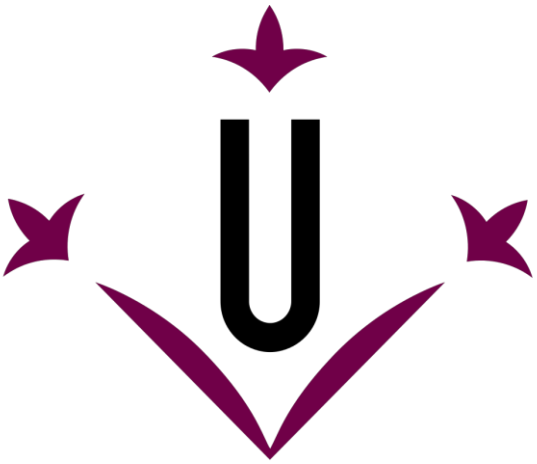

Universitat de Lleida

"Effectivity of high definition transcranial direct current stimulation (HD-tDCS) combined with therapeutic exercise treatment in athletic adult patients with chronic ankle instability. Prospective Double blinded randomized controlled trial."

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Abreviations list

CAI: Chronic ankle instability.

HD-tDCS: High definition- Transcranial direct current stimulation

NIBS: Non-invasive brain stimulation.

TMS: Transcraneal magnetic stimulation

ROM: Range of motion

LAS: Lateral ankle sprains

ATFL: The anterior talofibular ligament

M1: Primary motor cortex

TMS: Transcranial magnetic stimulation

tDCS: Transcranial direct current stimulation

RCT: Randomized controlled trial

CONSORT: Consolidated Standards of Reporting Trials

HPI: Hospital Jaume I de Castelló

HGC: Hospital General Universitari de Castelló

NRS: Numerical Rating Scale

HRQOL: Health related quality of life

DPA: Physically Active Scale

SPSS: Statistical Package for the Social Sciences

Abstract

Clinical research question: Is more effective therapeutic exercise combined with high definition transcranial direct current stimulation (HD-tDCS) than therapeutic exercise combined with sham HD-tDCS in athletic adult patients with chronic ankle instability (CAI)?

Objectives: To analyse the effectivity of high definition transcranial direct current stimulation (HD-tDCS) combined with therapeutic exercise in athletic adult patients with chronic ankle instability, compared to therapeutic exercise and sham HD-tDCS.

Methodology: ***Research design:*** A prospective, double-blind, randomized controlled trial (RCT) is designed in athletic adults with CAI. ***Sample:*** The sample will be formed by athletic adults diagnosed with CAI following the selection criteria of the International Ankle Consortium. ***Randomization:*** Subjects will be divided into two groups by means of balanced randomization performed with free software, simple randomization will be performed. Also, the patients and physiotherapist will be blinded and do not know in which group are. ***Intervention:*** There will be two groups, the experimental group treated with therapeutic exercise and real HD-tDCS and the control group treated with therapeutic exercise and sham HD-tDCS. The intervention is for 8 weeks and afterwards the patients will be followed during 8 weeks more. The treatment is divided in 3 stages in which the patients will overtake in proportion with their progression. ***Measures:*** There will be 7 assessment for the study patients. One before the rehabilitation start, two between intervention, another when the rehabilitation is finished and three more at 2,4 and 8 weeks respectively from the rehabilitation finish. The variables that are assessed are pain (NRS scale), motor control (Jump test), Health related quality of life (DPA scale) and ROM (My ROM app).

Keywords: Motor rehabilitation, Non-invasive brain stimulation, high-definition tDCS, therapeutic exercise, Chronic ankle instability.

Resumen

Pregunta clínica de investigación. ¿Es más efectivo el ejercicio terapéutico combinado con estimulación corriente directa transcraneal de alta definición (HD-tDCS) que el ejercicio terapéutico con estimulación cerebral en forma de placebo en pacientes adultos deportistas con inestabilidad crónica de tobillo(ICA)?

Objetivo: Analizar la efectividad de la estimulación corriente directa transcraneal de alta definición (HD-tDCS) combinada con ejercicio terapéutico en pacientes adultos deportistas con inestabilidad crónica de tobillo, comparado con ejercicio terapéutico y HD-tDCS placebo.

Metodologia: ***Diseño de investigación***: Ensayo prospectivo, doble ciego, aleatorizado y controlado (ECA) diseñado en adultos atléticos con ICA. ***Muestra***: La muestra estará formada por adultos deportistas diagnosticados con ICA siguiendo los criterios de "International Ankle Consortium". ***Aleatorización:*** Los sujetos se dividirán en dos grupos mediante una aleatorización realizada con software libre, se realizará una aleatorización simple. Además, los pacientes y el fisioterapeuta estarán cegados y no sabrán en qué grupo se encuentran. ***Intervención:*** Habrá dos grupos, el grupo experimental tratado con ejercicio terapéutico y HD-tDCS real, mientras que el grupo control será tratado con ejercicio terapéutico y HD-tDCS placebo. La intervención es de 8 semanas, luego los pacientes serán seguidos durante 8 semanas más. El tratamiento se divide en 3 etapas en las que los pacientes superarán en proporción con su progresión. ***Medidas:*** Habrá 7 evaluaciones para los pacientes del estudio. Una antes del inicio de la rehabilitación, dos durante la intervención, otra cuando la rehabilitación ha finalizado y tres más a las 2, 4 y 8 semanas, respectivamente, desde el final de la rehabilitación. Las variables que se evalúan son dolor (escala NRS), control motor (Jump test), calidad de vida relacionada con la salud (escala DPA) y ROM (My Rom app).

Palabras clave: Rehabilitación motora, estimulación cerebral no invasiva, tDCS de alta definición, ejercicio terapéutico, inestabilidad crónica de tobillo

1. Theoretical framework.

1.1. Introduction

"Lateral ankle sprains (LAS) are the most common musculoskeletal injury and contribute to a tremendous healthcare burden stemming from the high treatment costs" (1) with an annual healthcare cost for the management and treatment of ankle injuries estimated at over US$2 billion in United States (2). Is a very common injury because some studies report that 60% of the general population experience ankle sprains and (3) and up to 40% will chronify this injury and develop a condition known as chronic ankle instability (CAI) (4). In the UK, Cooke et al reported an average of 6.9 days of paid work lost due to lateral ankle sprain injuries, adding at least an additional £805 in lost productivity costs for each injury to the overall costs, compared with £135 of direct healthcare costs (5).

Chronic ankle instability is a heterogeneous injury in which individual patients present with unique combinations of pathomechanical, sensory-perceptual, and motor-behavioral impairments condition characterized by repetitive episodes or perceptions of the ankle giving way and is characterized by a patient's being more than 12 months removed from the initial LAS, with persistent symptoms such as pain, swelling, limited motion, weakness, and diminished self-reported function (4).

A systematic review and meta-analysis of prospective epidemiological studies indicate that the people group who have the highest risk for sustaining an ankle sprain are the females and children. In addition, the indoor and court sports are the activities in which the athletes experience more ankle sprains injuries. "The pooled estimate of ankle sprain incidence rate in high-quality studies is 11.55 per 1,000 cumulative units of exposure, giving a cumulative incidence rate of 13.6 sprains per 1,000 exposures for females versus 6.94 per 1,000 exposures for males"(6).

The data shows how the children experience more ankle sprains compared with adolescents (2.85 vs 1.94 per 1,000 exposures) and adolescents compared with adults (1.94 vs 0.72 per 1,000 exposures). This injury at a young age can negatively affect a child's ability to participate in activity and may trigger long-term sequelae such as early onset of osteoarthritis (6).

Is important understand the mechanism of injury by which the structures are damaged and for correct diagnosis and treatment (7). Historically, the reductionist approach often referred to as inversion ankle sprains, but this mechanism ignores the oblique axes of rotation of the talocrural and subtalar joints. Some studies analyse the kinematics of the injury mechanism and shown that the injury movement consists in both excessive inversion and internal rotation of the rearfoot on the tibia. In some athletes, the peak angles and angular velocities of inversion and internal rotation occurred not while the ankle was in plantar flexion but when it was in sagittal-plane neutral or dorsiflexed. This findings challenge the dogma of LASs as plantar flexion-inversion injuries.
For this reason, the term inversion–internal-rotation sprain would be a more apt kinematic description of the mechanism of injury for LAS (4).

1.1.1. Anatomy

The ligaments around the ankle can be divided, depending on their anatomic position, into three groups: the lateral ligaments, the deltoid ligament on the medial side, and the ligaments of the tibiofibular syndesmosis that join the distal epiphyses of the bones of the leg (tibia and fibula) (7).
The lateral collateral ligament complex consists of the anterior talofibular, the calcaneofibular, and the posterior talofibular ligaments. The medial collateral ligaments, also known as the deltoid ligament, are a multifascicular group of ligaments and can roughly be divided into a superficial and deep group of fibers (8).

The anterior talofibular ligament (ATFL) is the most frequently injured ligament of the ankle. This ligament limitate the anterior displacement of the talus and plantar flexion of the ankle (9). Despite the anatomical variants, this ligament is closely related to the ankle joint capsule and is typically composed of two separate bands. ATFL originates at the anterior margin of the lateral malleolus, it runs anteromedially to the insertion on the talar body immediately anterior to the joint surface occupied by the lateral malleolus. In plantar flexion, the inferior band of the ligament remains relaxed while the upper band becomes taut. In dorsiflexion, the upper band remains relaxed, and the inferior band becomes tight (9).
The calcaneofibular ligament originates from the anterior part of the lateral malleolus. It is anatomically positioned just below the lower band of the anterior talofibular ligament. The calcaneofibular ligament is the only ligament bridging both the talocrural joint and subtalar joint. Insertion of this ligament and its axis of rotation point allow flexion and extension

movements of the talocrural joint. The ligament is relaxed in the valgus position and tense in the varus position. This explains the potential for injury even without dorsiflexion-plantar flexion movement in the ankle(7).

The posterior talofibular ligament originates from the malleolar fossa, located on the medial surface of the lateral malleolus, coursing almost horizontally to insert in the posterolateral talus. In plantar flexion and in the neutral ankle position, the ligament is relaxed, while in dorsiflexion, the ligament is tensed. Due to the multifascicular aspect of this ligament, it inserts not just in a specific area. (7)

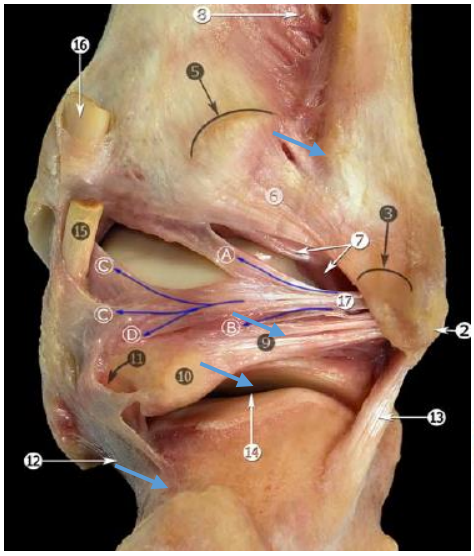

Figure 1 Posterior view of the anatomic dissection of the ankle.

Nº 13: Calcaneofibular ligament;

17: Posterior intermalleolar ligament

Figure 2 Osteoarticular anatomic dissection of the lateral ligaments of the foot and ankle joint.

Nº 4: Distal fascicle of the anterior tibiofibular ligament; 5: Superior band of the anterior talofibular ligament; 6: Inferior band of the anterior talofibular ligament; 10: Calcaneofibular ligament.

1.1.2. Ligament healing.

The ligament healing is very similar to the tendon because structurally and physiologically share many similarities. The difference in the extracellular matrix (ECM) composition and organization varies with each individual tendon and ligament according to anatomic location, presumably due to variations in the mechanical loading environment (10).

Acute injury to a ligament is followed by rapid initiation of the healing process. This process is generally subdivided into three chronological stages: inflammation, proliferation, and remodelling(10).

The inflammatory stage: In this phase, the clot serves as the initial scaffold for the recruited extrinsic inflammatory cells. This inflammatory cells release growth factor-β (TGF-β), insulin-

like growth factor-I (IGF-I), and platelet-derived growth factor (PDGF), causing local inflammation. Elaboration of these growth factors recruit neutrophils, which in turn activate macrophages to phagocytose necrotic debris. Approximately 2 days following injury, these cytokines released from macrophages and intrinsic cells of the ligament initiate the proliferative stage by recruitment of fibroblasts(10).

The proliferative phase: Is characterized by expansion of the ECM, increased cellularity, and deposition of fibrovascular scar by fibroblasts. IGF-I and TGF-β expression remains high, continuing to attract fibroblasts to the site and increase ECM production. Collagen synthesis is a highly oxygen-dependent process, underlying the importance of synergistic angiogenic actions of bFGF and VEGF in this stage of healing. This growth factos stimulate angiogenesis to provide extrinsic cells, nutrients, and additional growth factors to the area of injury(10).

About 2 weeks following injury, remodeling of the injured area begins with reorganization of the newly deposited collagen. This process overlaps with the proliferative phase, leading to a gradual decrease in cellularity and increase in a fibrous matrix. Tenocytes and collagen fibers become aligned in the direction of stress, increased action of collagenases aid in the resorption of type III collagen and replacement with type I collagen, which has more crosslinks and tensile strength. This process continues for months and years following the injury (10).

1.1.3. Body Self-Organization at different levels of analysis that lead LAS to CAI.

After an LAS, patients quickly develop the clinical signs and symptoms of pain, swelling, and inflammation. Simultaneously, but often less obviously, alterations in sensorimotor function also occur. The injury also initially triggers sensorimotor changes via inflammatory and pain mediators that result in specific sensory-perceptual and motor-behavioral impairments. Together, the injured tissues, accompanying inflammatory responses, and the patient's psychological and emotional responses to the injury (eg, pain and mechanical and sensorimotor alterations in response to ligamentous injury) drive the specific impairments that can cause an individual to deviate from successful healing toward CAI " (4).

Commonly, the clinicians could underrate this injury. Nevertheless, if the treatment do not correlate with the time healing of the tissue and do not consider the biopsychosocial model of the injury there could have been some impairments that lead to CAI (4,11).

Following the dynamic systems theory, which provides a framework for explaining how the sensorimotor system develops strategies to accomplish movement goals, the human body is a system composed of many subsystems that are non-linear and interact dynamically. The amount of movements (degrees of freedom) can be organized in a variety of ways to accomplish movement goals. In this way, multilevel components (cells, tissues, systems, organisms, and social constructs) interact between them reorganizing the movement in relation with the constraints (individual, task and environmental). This is why we see different adaptations in chronic injuries(12).

1.1.4. Local level

After an acute LAS, at least, the lateral ligaments of ankle have been damaged, this increase the organismic constraints, acting on the sensorimotor system and significantly hindering the sensorimotor system's ability to accomplish movement goals (1,11,13). The thickness of the ATFL (patients with CAI have substantially ATFL thicker than healthy controls), alterations in the osteochondral surface of the talus and modifications of the intrinsic foot muscles volume. This structural changes may be contributing to specific impairments(14). Also, the ankle range of motion (ROM) is restricted (1), the muscles around the ankle are weak and somatosensation is altered(4,15). The CAI patients inability to accurately sense the position of their ankle joint before initial contact during gait or landing has been theorized to increase the risk of recurrent ankle sprain (4). The diminished somatosensation occur due to damage to the ligamentous and articular proprioceptors during injury and possible nerve injury secondary to ligament injury, the inability of patients with CAI to accurately sense the position of their ankle joint before initial contact during gait or landing has been theorized to increase the risk of recurrent ankle sprain. The ability to integrate different sensory inputs appears to be compromised in CAI (4).

Song et al performed a metaanalysis to investigate postural control in eyes-open and eyes-closed positions. Compared with healthy controls, patients with CAI relied more heavily on visual information than somatosensory information during unipodal-stance balance tasks and have more difficulties to reweight dynamically(15). "However, more recently, this feedback-based mechanism has been challenged because on its own it is unable to explain all phenomena that are associated with CAI. For example, patients with unilateral CAI were shown to suffer from bilateral deficits in single-limb balance" (16).

The perception-action cycles are changed due to ankle injury (organismic constraint) and in order to cope with daily tasks the motion patterns are altered. This movement solution introduces unfamiliar signals into the nervous system, thereby producing unaccustomed perception-action cycles (11,17). Failure to address specific impairments post injury can lead to longstanding constraints that normalize altered movement patterns, resulting in chronically altered perception-action cycles and a neurosignature that predisposes an individual to recurrent episodes of the ankle giving way and ankle sprains(4).

Loss of the structural integrity of the lateral ankle ligaments results in pathologic laxity of the talocrural joint and possibly the subtalar joint. Evidence of an initial increase in laxity after acute LAS and a subsequent return toward preinjury laxity in the weeks and months afterward has been reported in a few prospective studies; some residual laxity is likely to remain in most patients who incur an LAS(18,19).

In contrast to pathologic laxity, particular accessory joint motions may be limited after LAS or with CAI. Restrictions in anterior-posterior glide of the talus on the tibia have been well documented as being associated with limited osteokinematic dorsiflexion of the talocrural joint in patients with lateral ankle instability (4).

Furthermore, many patients have demonstrated anterior displacement of the distal fibula relative to the tibia and associated restriction of anterior-to-posterior glide of the distal fibula(20).

1.1.5. Mesoscopic level

The self-organization is done in other body levels and are related to the altered motion patterns. CAI is not only related to sensory deficits but is also associated with changes in the eferent motor control that contribute to motor-behavioral impairments(16,21).

The eferent control of motor tasks greatly relies on the activity of supraspinal motor centers and of spinal reflex circuitries (16). A large body of literature has examined muscle-contraction timing and amplitude response to inversion perturbations of the ankle, in a meta-analysis Hoch and Mckeon found delayed reaction time of the fibularis longus and brevis muscles in reaction to sudden inversion perturbations in patients with CAI(22). In addition, arthrogenic muscle inhibition has been reported in CAI most often by assessing the H-reflex response in the fibularis longus muscle and soleus. This inhibition is not observed only in muscles surrounding ankle joint, because investigators observed that patient with unilateral CAI had bilateral inhibition of the hamstrings muscles and ipsilateral facilitation of the quadriceps muscles

compared with healthy controls, as well as impaired contractility of the diaphragm indicating that proximal muscle function was affected not only in the lower extremity musculature but also in the trunk (23). The muscle synergies are self-organized and adapted to the new constraints (19).

" Neuroplastic changes are reflective of adaptive neurophysiological processes occurring as the result of altered afferent stimuli including nociceptive and neuropathic transmission to spinal, subcortical and cortical areas with MSD that are initially beneficial but may persist in a chronic state, may be part and parcel in the pathophysiology of the condition and the development and maintenance of chronic signs and symptoms (24)."

The influence of supraspinal motor control in patients with CAI has been studied using measures of motor-cortex excitability and inhibition. Recent paradigm shifts in joint instability etiology at both the ankle and knee have identified changes within the central nervous system that alter motor planning, generating movement patterns that predispose individuals for re-injury. Kosik et al in 2016 identified less fibularis longus recruitment map volume and area in the motor cortex among patients with CAI than healthy individuals, suggesting that the former had a more concentrated and restricted area of neurons able to recruit the fibularis longus muscle (25).

Sensory testing has demonstrated changes in sensory transmission and processing across a number of muscoloskeltal disorders including osteoarthritis (OA), Patella-Femoral Pain Syndrome, tendinitis, Lateral Epicondylitis, Carpal Tunnel Syndrome, and cervical injuries including whiplash (24,26–28).

Also, other patients with musculoskeletal pain like low back pain, in comparison to healthy individuals, have functional changes (reorganization) of the neuronal properties in the sensorimotor system representing the muscles most affected by pain(26). The patients have reduced cortical spinal drive in the lumbar spinal muscles (27) and a shift in the representation of the lower back muscles in the somatosensory cortex.

Specifically, individuals with CAI and those with anterior cruciate ligament injury demonstrate decreased excitability of the primary motor cortex (M1), altered somatosensory cortex activation in response to joint loading, and utilize increased activation of visual and planning areas in simple movement execution when compared to uninjured controls (3).

"Transcranial magnetic stimulation (TMS) studies have shown that athletes with patellar tendinopathy (PT) have greater M1 excitability than pain-free jumping athletes, as reflected in

larger evoked muscle responses in the quadriceps (rectus femoris; (28))." As stated, athletes with PT also have greater cortical inhibition than healthy controls have. This confirm that not all the injuries have the same self-organization because patients with CAI have less M1 excitability in the representation of fibularis longus. These preliminary findings appear to replicate the findings of unilateral stroke that affects the M1, in particular the plausibility of greater interhemispheric inhibition and involvement of bilateral changes (26).

In other hand, muscle weakness have been reported of the proximal and distal muscles. During walking, patients with CAI tend to exhibit greater inversion and plantar flexion of the foot relative to the tibia, a more laterally deviated center of pressure throughout stance (29,30).

Findings from meta-analyses indicate ankle invertor and evertor and knee extensor muscle weakness, in individuals with CAI compared with controls. While studies of hip strength are limited, individual study data also suggest lower hip flexor, abductor and external rotator strength in individuals with CAI than controls(31).

1.1.6. Macroscopic scale and environmental factors

Environmental factors include societal expectations the individual perceives regarding physical activity and sports participation as well as expectations for his or her role in home, family, work, and transportation activities(4). These factors play a great role in the rehabilitation and the physiotherapist must have care with all of these factors because social relations, pain interpretations, rehabilitation expectative have incidence in the injury evolution.

Fears of movement and re-injury during functional activities have been reported in patients with CAI. The perception that movement of the involved ankle will be harmful runs counter to the emphasis on therapeutic exercise as a primary treatment for CAI and represents an important obstacle to be managed when treating this condition. Also, reduced self-reported function and health-related quality of life have been measured in patinets with CAI(4,32).

Some patients choose to alter their physical activity to avoid symptoms or recurrent sprains. Reduce physical activity leads not only to disminished quality inputs to the tissue that is reparing, also to long-term problems like arterial hypertension and other health problems. In study done with college students, those that have CAI took more than 2100 fewer steps per day than healthy individuals with no history of ankle injury(33).

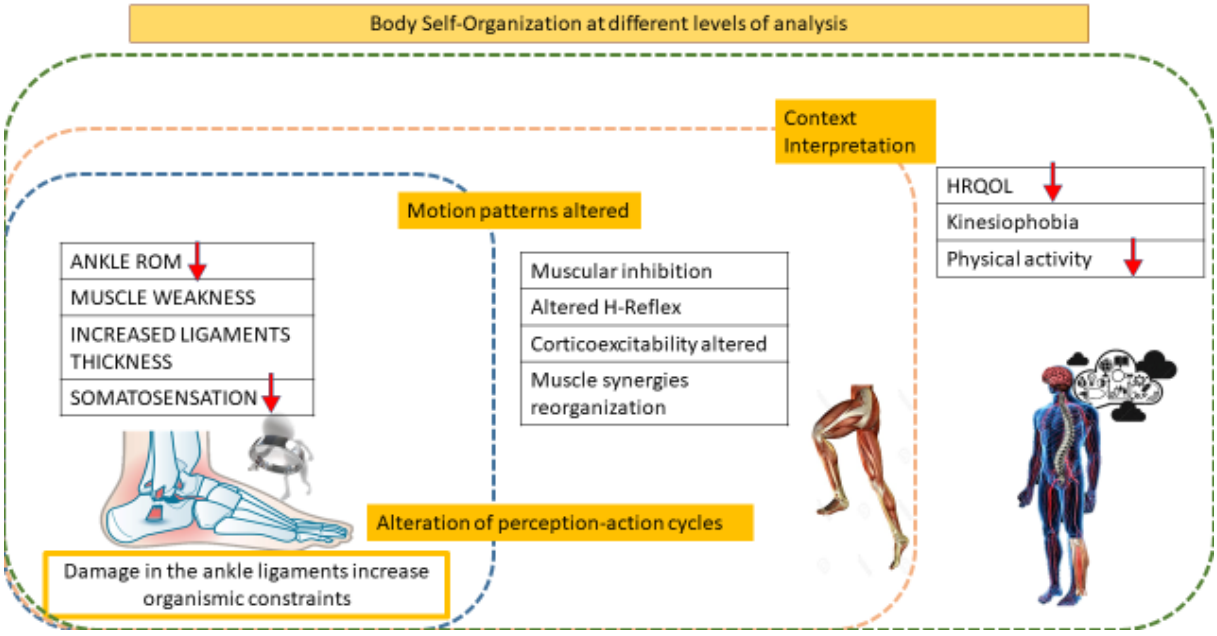

Figure 3 Body self-organization at different levels of analysis ((1,4,11,16)

1.2. Surgical treatment vs Conservative treatment.

In front of the amount of signs and symptoms presented by CAI patients, there are two options preferently. Conservative or surgical treatment.

Conservative treatment (rehabilitation, taping, brace) may reduce "giving-away" episodes and the occurrence of recurrent ankle sprains, is effective in managing CAI(34). Strength training of the muscles around the ankle with well-planned proprioceptive exercises helpe the patients return to normal living and sports activities, and prevented unnecessary surgery, especially in cases with functional instability. In other hand, there is no consensus regarding optimum surgical treatment for CAI(34).

Structural damage to musculoskeletal structures alone cannot always fully explain the presence of signs and symptoms in chronic musculoskeletal disorders (24). As other studies reported , in some musculoskeletal conditions the responsiveness and somatotopic organization in S1 and M1, including changes in excitability and the representation of the muscles are present(24,35,36). Also, patients' perceptions of the level of their disability and beliefs about the pain have influence in the patient's pathology.

For this reason integral rehabilitation, treating the disorder from different sides (biopsychosocial paradigm), is a must in patients with CAI because the structure could be healed (surgery) but the impairments could be present (4,24).

1.3. Non invasive brain stimulation (NIBS)

Transcranial electrical stimulation has recently attracted considerable scientific interest due to its ability to modulate brain functioning (37). Currently, the most used stimulation devices can be divided into invasive techniques, such as deep brain stimulation (DBS), and non-invasive brain stimulation (NiBS) techniques, whose most representative methods are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)(35). DBS is a technique that needs the implantation of the electrodes on the stimulated area, which is associated with the typical risk derived from surgery, as infections. Therefore, there is an increasing tendence on the search for non-invasive brain stimulation techniques, which can modulate the motor function avoiding those risks(35).

In relation with the principal NIBS, tDCS when compared with TMS, electric current induced by tDCS is not focal. Hence, it possibly stimulates not only M1, for instance, but also adjacent areas, consequently losing some precision. Furthermore, while TMS induces an action potential, tDCS does not induce one, but only facilitate its triggering as the constant current fields produced by tDCS are not sufficient to promote the fast depolarization required to induce an action potential in neural membranes. Therefore, tDCS is only able to decrease/increase the membranes' threshold and thus, it modulates neural excitability(36).

The stimulation facilitates or inhibits spontaneous neuronal activity resulting in cortical excitability modulation, and neuroplastic reorganization (37,38). TDCS has been used in neuropsychiatric and neurological disorders, modulation of autonomic nervous system, appetite, energy expenditure, motor performance and motor learning (37,39,40).
In relation with how induce neuroplastic changes, some studies have suggested that tDCS could have an effect on neuronal synapsis' strength, altering the activity of NMDA and GABA receptors, thus triggering plasticity process, such as long-term potentiation and long-term depression (36). Neuroimaging study showed blood flow changes following stimulation, which may be related to a direct effect of tDCS over blood flow, with an increase in oxygen supply on cortical areas and subsequent enhancement of neuronal excitability (36). Given these

mechanisms, tDCS seems to be a potential valuable tool to stimulate brain activity and plasticity following a brain damage.

To date, there is no evidence of severe adverse events following tDCS in healthy individuals, as well as in patients with neurological conditions, such as stroke. Moreover, the advantages of tDCS over these methods include the ease of use, its safety, portability, the nonexisting risk of addiction and especially, its long-term effects.

One of the principal lacks of tDCS is the extension of the area that results stimulated during its application. demand, a recent improvement of the present technique, namely high definition transcranial direct current stimulation (HD tDCS), has emerged in the field of neuromodulation presenting considerable enhancements. The new configuration of HD tDCS also allows the settlement of more than one anode and cathode, which appears to result in a mayor effect of tDCS and an increase of focality(35,41). HD tDCS is a promising technique that improves the neuromodulation in terms of focality, plasticity and security(35). HD-tDCS was developed with arrays of smaller "high-definition" electrodes to increase brain modulation accuracy. Delivery of HD-tDCS is capable of inducing significant neurophysiological and clinical effects in both healthy subjects and patients(37).

1.4. Justification.

There are some amount of evidence that in different musculoskeletal disorders reported neuroplastic changes in the brain resulting in changes in corticospinal excitability(36,37,40).

Specifically in patients with CAI there is an organization of the body subsystems to cope with the daily activities and the increased organismic constraints(4,11,19,25). In this way therapeutic exercise has become in the treatment election to restore the functionality of the entire system because improve substantially all the impairments that are present in CAI(34). For example, decreased corticoexcitability, neuromuscular inhibition, ankle ROM decreased, HRQOL is disminished and others that are interrelated (4,19).

More recently, NIBS has become in tools to enhance brain conections and improve the rehabilitation process and outcomes of different neurological disorders like Parkinson, strokes or others neurological disorders (35,37,41,42). One type of NIBS is tDCS that has been investigated over the years due to its short and also long-term effects on cortical excitability and neuroplasticity(36), also has been used in the treatment of CAI with promising results (3). In recent years, HD-tDCS have improved the lack of focality of tDCS bringing effectivity,

safety and portability(35). Also, there have been developed sham condition for HD-tDCS (43) and softwares (Hd-Explore) that allow doubl-blind studies and improves study internal validity.

In this way, therapeutic exercise and HD-tDCS are techniques with efficacy proved in chronic musculoskeletal disorders and are safe for the patient (34,35). This combination could reduce the different impairments showed in patients with CAI and improve the outcomes in regard to motor control, pain, ROM, HRQOL, and self reported quality of life at the finish of rehabilitation.

2. Hypothesis.

The investigation hypothesis is that the HD-tDCS combined with therapeutic exercise is more effective in the treatment of the chronic ankle instability in athletic adult patients by modulation of neuronal excitability and brain plasticity compared to therapeutic exercise and sham HD-tDCS.

3. Objectives.

3.1. Principal Objective.

To analyze the effectivity of high definition transcranial direct stimulation (HD-tDCS) combined with therapeutic exercise in athletic adult patients with chronic ankle instability, compared to therapeutic exercise and sham HD-tDCS.

3.2. Secondary Objectives.

- Assess in athletic adult patients with chronic ankle instability (CAI) the effectivity of HD-tDCS combined with therapeutic exercise compared to evidence based therapeutic exercise improve the health-related quality of life.
- Evaluate the evolution of ankle range of motion (ROM) in the experimental group during the combined treatment of HD-tDCS and therapeutic exercise.
- Evaluate the strength evolution of fibularis longus and brevis in the experimental group during the combined treatment of HD-tDCS and therapeutic exercise.
- To compare between the experimental and the control group the function and pain in patients with CAI.

4. Methodology.

A prospective, double-blind, randomized controlled trial (RCT) design was used in this study. Randomized controlled clinical trials (RCTs) are the gold standard for ascertaining the efficacy and safety of a treatment. RCTs can demonstrate the superiority of a new treatment over an existing standard treatment or a placebo. In clinical research RCTs are used to answer patient-related questions, and in the development of new drugs they form the basis for regulatory authorities' decisions on approval(44).

We follow The CONSORT (Consolidated Standards of Reporting Trials) Statement that was developed to help authors report randomised controlled trials. It has improved the quality of reports in medicine, and has been officially endorsed by over 600 journals and prominent editorial groups(45).

In other part, we want to supervise the effects of our intervention over the time, because is important to know if the patients have improve the pain and motor control along the time. This is the reason why we choose to screen the patients weeks after the trial is finished.

4.1. Study participants.

The study population will be athletic adults (18 to 65 years old) that are diagnosed with chronic ankle instability in " Hospital Jaume I de Castelló" (HPI) and " Hospital General Universitari de Castelló"(HGC) following the selection criteria of the International Ankle Consortium (Annex 1) from 1st of October 2020 to 31st of October of 2020. Also, e-mails to sport federations and clubs are sent to inform that if any athlete have the symptom of "ankle giving-way" and want to participate in the study could come to the hospital to screening them.

Then, potential participants received a brief telephone from the principal investigator to verify basic eligibility. Moreover, were scheduled for a full in-person screening, at which time we also obtained written informed consent.

4.2. Sample

The sample size was calculated using the Granmo calculator v.7.12. Based on the analysis of the variance of means, and estimating an alpha risk of 5% (0.05), a beta risk of 10% (0.10), a unilateral contrast, a typical deviation of 10% (0.10). The calculation will be based in the study of Ross and Guskiewicz (46) that Assume (2.33 +/- 0.33 seconds; $P < 0.001$) like relevant significant in the jump test.

4.3. Inclusión variables:

- Patients with CAI diagnosed with selection criteria of the International Ankle Consortium(4,25).
- Informed consent signed.
- Practicing any sport before CAI.
- 18 to 65 years old

4.4. Exclusión variables:

For participant safety, certain medical conditions were exclusionary(42):

- Current cancer.
- Infection.
- History or current evidence of neurological disorder (e.g. epilepsy, major depression, stroke, neuropathy, neuropathic pain)(47).
- Uncontrolled medical problem.

For HD-tDCS safety(42):

- History of skull trauma.
- Intracranial surgery
- Implanted hardware, or metal in the cranial cavity
- The presence of broken skin or other dermal lesions where HD-tDCS electrodes would be placed.

As risks of HD-tDCS to an unborn fetus are unknown, pregnant women were also excluded (42,47).

4.5. Aleatorization

Subjects will be divided into two groups by means of balanced randomization performed with free software (https://www.randomizer.org/). The randomization sequence will only be performed by the principal investigator and auditor.

A good experiment or trial minimizes the variability of the evaluation and provides unbiased evaluation of the intervention by avoiding confounding from other factors, which are known and unknown. Randomization ensures that each patient has an equal chance of receiving any of the treatments under study, generate comparable intervention groups, which are alike in all the important aspects except for the intervention each groups receives. It also provides a basis for the statistical methods used in analyzing the data(48).

We use simple randomization, This randomization approach is simple and easy to implement in a clinical research. In large clinical research, simple randomization can be trusted to generate similar numbers of subjects among groups. However, randomization results could be problematic in relatively small sample size clinical research, resulting in an unequal number of participants among groups(48). For this reason, we collect sociodemographic variables for ensure that both groups (experimental and control) have heterogeneity.

When the aleatorization is done, the principal investigator will communicate to subjects the schedule and the physiotherapist of the intervention. In addition, principal investigator with statistic collaboration will programme the HD-tDCS stimulator with HD-Explore™ software to provide real or shame stimulation, each participant have one number and automatically when the pimary care physiotherapist pulse their numbers in the software, the HD-tDCS a provide real or sham stimulation.This work is done with the statistic and ensure that both the patients and physiotherapist are blinded.

4.6. Study variables

	Variable	**Measurement instrument**	**Methodological criteria**
INDEPENDENT	CAI Treatment.	HD-tDCS + T.exercise/T. exercise	Categorical (nominal)
	Age	Questionnaire	Discret (Quantitative)
	Sex	Questionnaire	Categorical (dichotomous)
	Sport	Questionnaire	Categorical (nominal)
DEPENDENT	Pain	NRS	Discret (Quantitative)
	Motor control	Jump test.	Continuous (Quantitative)
	HRQOL	DPA scale	Continuous (Quantitative)
	ROM	My ROM app	Continuous (Quantitative)

Table 1 Study variables

4.7. Dependent variables:

4.7.1. Pain

Pain is a hallmark of most chronic musculoskeletal conditions. However, In CAI literature pain has received relatively little attention (49) ,although clinical experience tells us that persistent pain is a common reason for patients with CAI to seek health care (4). Chronic psychological and physical stress associated with chronic pain can further diminish a patient's ability and willingness to participate in functional activities(17,50).

Ankle injuries increase the organismic constraints acting on the sensorimotor system and significantly hindering the sensorimotor system's ability to accomplish movement goals (19). The chronic pain is part of the system self-organization process when the sensorimotor system is impaired. This lead to functional change at all level of analysis, from macroscopic level such as daily physical activity patterns (33) and reduced quality of life (51) to microscopic level as change in M1 representation of fibularis longus(25).

It is plausible that such strategies benefit CAI individuals by reducing pain and re-orienting sensory information for the maintenance of postural control. Pain and perceived instability explained a significant proportion of changes in spinal-level sensorimotor control (52).

For assess the pain, the Numerical Rating Scale (NRS) is a subjective measure in which individuals rate their pain on an eleven-point numerical scale. The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain)(53). It has been shown that a composite scoring system including best, worse, and current level of pain over the last 24 hours was sufficient to pick up changes in pain intensity with maximal reliability (54).

When compared with the Visual Analog Scale and Visual Rating Scale, NRS had better compliance in most of studies, better responsiveness and ease of use, and good applicability.The recommendation was that it should be measured by a 0–10 NRS with the standard endpoints "no pain" and "pain as bad as you can imagine," with clinically meaningful time frames(55).

NRS requires the patient to rate their pain on a defined scale. For example, 0–10 where 0 is no pain and 10 is the worst pain imaginable. We use 11 point scale because Jensen et al (1996) report that were sensitive enough to measure chronic. Other advantages of NRS are that

they are easily understood and quickly administered (56). They have been reported to be sensitive to change and correlate well with other pain intensity measures (57).

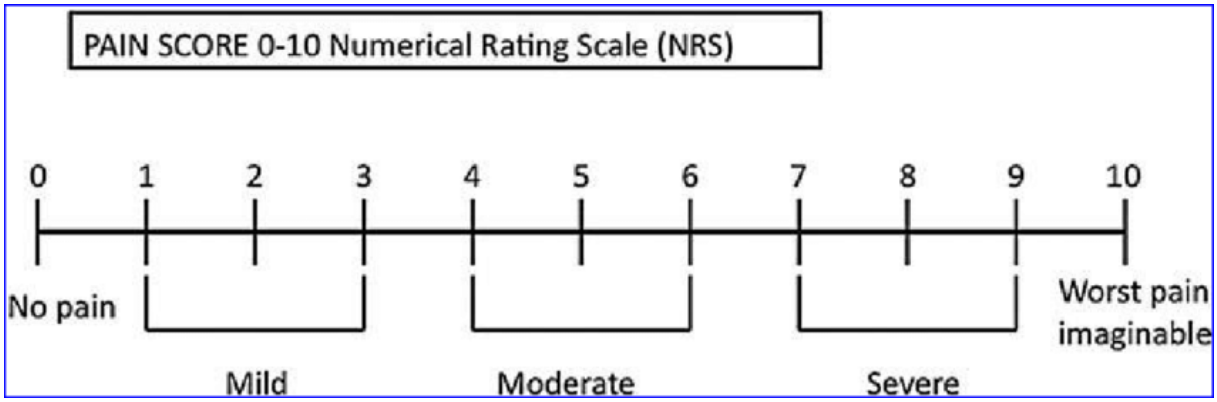

Figure 4 Numeric rating scale from Marrazzu et al. (58)

4.7.2. Motor control.

The sensoriomotor impairments are related to functional instability and recurrents reports of 'giving way' episodes at the ankle joint that constitutes the characteristic features of chronic ankle instability (CAI)(59).

The functionality of the ankle is affected by the reaction time of the muscles. It has been found that there are delayed reaction time of the muscles like fibularis longus and brevis muscles in response to sudden inversion perturbations with CAI (22). Also, neuromuscular inhibition Several groups have reported diminished H-reflex amplitude in the fibularis longus and soleus(60). Nevertheless, the hipoactivation is not only in the muscles that surround the ankle, investigators observed that patients with unilateral CAI had bilateral inhibition of the hamstrings muscles and ipsilateral facilitation of the quadriceps muscles compared with healthy controls (23).

Dynamic postural stability has been defined as maintaining balance while transitioning from a dynamic to a static state (6). Time to stabilization, the only previous method of quantifiably assessing dynamic postural stability, has detected differences between stable and FAI patients (61). For this reasons assess the motor control and the muscles activation time is important for know if the functionality is impaired.

The jump protocol was performed as first described by Ross and Guskiewicz (46). Subjects stood 70 cm from the center of the force plate and jumped with both legs to touch an overhead

marker placed at a position equivalent to 50% of each subject`s maximum vertical leap before landing on one leg on the force plate. Maximal jump will be assessed with MyJump App2 (62). Each subject was instructed to jump with one`s head up and hands in a position to touch the designated marker. Subjects were instructed to land on the test leg, stabilize as quickly as possible, and balance for 15 seconds with hands on one`s hips while looking straight ahead. If a subject lost balance and touched the floor with the contralateral limb, the trial was discarded and repeated. Likewise, if a short additional hop occurred on landing, the trial was discarded and repeated(61). A Bertec triaxial force plate (Bertec Corporation, Columbus, OH) was used to collect the baseline and jump-landing data.

Also, participants will be instrumented with EMG sensors (Bagnoli-4, Delsys Inc., Boston, MA) over the tibialis anterior, peroneus longus, and soleus as described in Bruce et al. 2019 (3) All data were analyzed offline in separate LabVIEW software. Postural stability indices were calculated in the anteroposterior (APSI), mediolateral (MLSI), and vertical (VSI) planes, as well as a composite score (DPSI) described by Wikstrom et al (61). EMG data were extracted 250ms prior to landing and 250ms following force plate contact (3). Analog force and EMG data were synchronized and collected in custom LabVIEW software at 1000 Hz.

4.7.3. The Disablement in the Physically Active scale

Measures of health related quality of life (HRQOL) are diminished in patients with CAI (63,64). The impairments of CAI are thought to contribute to long-term limitations and restrictions in recreational and occupational activities that consequently affect HRQOL(64).

HRQOL focuses on broader concerns, such as mood, vitality, and social interactions, that are not as directly linked to ankle function as are the items on region-specific function scales. The most commonly used HRQOL scales in medicine are the Short Form-36 and Short Form-12 questionnaires (4).

A criticism of the Short Form scales is that they may not be appropriate for athletic or otherwise highly physically active populations because of a ceiling effect in their psychometric properties (65). In response to this weakness, the disability in the Physically Active Scale (DPA) (Annex2) was developed to more accurately assess HRQOL in this population.

The Disablement in the Physically Active scale , a population-specific patient reported outcome (PRO), was developed to evaluate constructs of disability in physically active populations (66).

The DPA scale consists of 16 statements rated by the patient on a 6-point Likert scale, ranging from 0 (no problem) to 5 (severe) (67). Patient disablement is assessed by summing the scores of each item and then subtracting 16 points. Total scores range from 0 (no disablement) to 64 (highest level of disablement) (32). Initial psychometric evaluation of the instrument included assessment of internal consistency (ie, Cronbach a) and reliability (ie, intraclass correlation coefficient). Cronbach a scores for the DPA were high in the acute (0.908)- and persistent (0.890)-injury groups. The intraclass correlation coefficient (95% confidence interval) of the DPA scale was excellent (0.943 [0.885, 0.972])(32).

4.7.4. ROM

Individuals with restricted dorsiflexion ROM have been shown to have an increased risk of sustaining a LAS when compared to individuals with normal dorsiflexion ROM(68,69).
Regardless of the underlying link between LAS and CAI dorsiflexion ROM deficits, evidence suggests that both patients with an acute LAS and CAI can be screened for decreased ROM and treated for arthro- or osteokinematic restrictions as suggested by Hertel's treatment paradigm for patients with CAI (1,4).

MyROM app is useful tool for assess the ROM of the ankle.
There was an almost perfect correlation between the digital inclinometer and the Dorsiflex app for the measurement of ankle dorsiflexion (r=0.989, 95% CI=0.986-0.993, SEE=0.48º), with trivial, non-significant differences between devices (SMD=0.17, p=0.10). When analyzing the reliability of the app for the measurement of five different trials for each participant, similar coefficients of variation (CV) were observed in comparison with those obtained with the digital inclinometer (Dorsiflex app: CV=5.1±2.3 %; Digital inclinometer: CV=4.9±2.5 %) (70).

4.8. Data collection

The first screening will be done by the primary care physiotherapist at the " Hospital Jaume I de Castelló" and " Hospital General Universitari de Castelló", they derived the possible candidates for the study following the study exclusion and inclusion selection criteria.

Then, potential participants received a brief telephone from principal investigator to verify that the person is able to participate in the study and and will be scheduled for a full in-person screening. Then, the principal investigator evaluate the exlusion and inclusion criteria are correct in the study participants, at which time we also obtained written informed consent and the aleatorization will be done.

At this time, before start the study, extern examinators will be done the assessment of the dependent study variables (DPA scale, ankle ROM Jump test, and NRS for pain).

When rehabilitation process start, the extern examinator will assess the patients when the primary care physiotherapists accept that the patient is able to pass to other phase in the rehabilitation process.. Functional criteria is chosen in the assessment to pass to next stage rehabilitation instead of time criteria, because each patient have different evolution.

When the training will be conclude the patients will be assessed again. The dependent variables assessment will be done by other hospital examinators that are extern to the study. They have experience in this type of assessment and they have overcome pilot test for assess the measurement variability between subjects and examinators. The examinators will be use sheet standardized where they must record all the data of the assessment.

The data collected must be documented anonymously and dissociated, linked to ordinal number, so that only the principal investigator can identify the participants.

The same assessment procedure will be performed 2, 4 and 8 weeks later since the study will be finished. Only took part for the study those participants that complete all the process without incur in other injuries or relapse.

4.9. Generalization and aplicability:

We hypothesized that while evidence based training would contribute to improvements across all participants, the individuals receiving HD-tDCS could demonstrate earlier, greater, and more durable improvements in outcome variables. Therefore, the improvement in motor control, pain and patient disablement could diminished the social and daily problems of the CAI, enable athletes to continue their sports career.

The results of this study would provide a foundation on which further clinical trials aimed at modifying joint injury rehabilitation paradigms could be based.

On the other hand, if HF-tDCS is succesfull improving the rehabilitation of athletes. Is a tool which could be very useful for sports team or physiotherapy private center because is a type of NIBS that is portable, cheap and easy to use. Even is possible its application in different contexes,during the motor training and even combined with aerobic exercise(35).

The results of this study will be applicable to amateur or elite athletes of all disciplines between 18 and 50 years old that are diagnosed with CAI. Although this exercise program combined with NIBS could be used as prevention after one ankle sprain, to diminished the probability to chronify the injury.

In the case that the results do not be significative or not correlate to the study hypothesis, this will significate that HD-tDCS will not be selection treatment for CAI. In other part, for investigators will serve to study other types of NIBS or other combinations HD-TDCS to stimulate different brain parts or with other intensities, for example.

4.10. Statistic analysis.

Stadistic analysis will be performed with IBM SPSS (Statistical Package for the Social Sciences) version 24.0 for Windows.

Using descriptive statistics, the aim is to accurately expose the data and characteristics of the subjects participating in the study, and will allow to analyze the sample data by the classification, graphic representation and then the with statistical inference we will study the possible generalization of the results obtained in the sample of the study to the general population.

For the continuous quantitative variable, will be done univariate analysis and calculated characteristic measures, which are classified into four groups: trend measures central (mean, median, and mode); dispersion measures (variance, standard deviation and range); position measurements (percentile and quartile); and shape measurements (asymmetry and curtosis). For the graphical representations, for continuous quantitative variable it will be used the histogram(71). In other part for categorical variables, frequency tables will be created, in which records the absolute frequency, relative frequency, cumulative absolute frequency, and cumulative relative frequency

Bivariate analysis is the simultaneous analysis of two variables (attributes). It explores the concept of relationship between two variables, whether there exists an association and the strength of this association, or whether there are differences between two variables and the significance of these differences. The correlation coefficient between two continuous-level variables is also called Pearson's r or Pearson product-moment correlation coefficient. If we do not assume normal distribution Mann- Whitney Test will be perfomed(72).

Regarding statistical inference, the confidence interval will be 95%, thus assuming a 5% error. Depending on the values obtained and on this statistical inference, the null hypothesis stated will be accepted or rejected previously.

4.11. Intervention plan

4.11.1. Control group:

The experimental group intervention consists in the combination of HD-Tdcs and the framework proposed by Mckeon et al. in 2019 (11) that is focused in the perceptual framework for conservative treatment and rehabilitation of ankle sprains. This theoretical framework tries to integrate the evidence from systematic reviews and best-practice recommendations with the emerging paradigms in perception, the dynamics of skill acquisition, and the biopsychosocial model of function, disability, and health.

The key concept discussed throughout is the interdependence of the perceptions of cells and tissues, the body, the perception of self, and the perception of self in the context of society.

The impairment of ankle ligaments could affect this interdependence because the motor control is subservient to the available relevant sources of sensory information(73), however, when this occur, the body will self-organize to find a motor strategy that circumvents organismic constraints to accomplish the tasks that one deems necessary. But if altered movement patterns are normalized, could result in chronically altered perception –action cycles and neurosignature (4). Whereas the initial sensory alterations due to tissue damage in the periphery may resolve over time, the altered neurosignature patterns may remain. This may explain the continuum of disability experienced by those with CAI long after the injury has resolved(19).

Disability then emerged as a biopsychosocial pattern of behavior of long-term impairments and functional limitations in the context of the patient's perception and the perception of the society to which he or she belongs (11).

Rehabilitation goals should no longer focus on regaining appropriate action (increasing strength, balance, power) but rather on enhancing the patient's perception and influencing advantageous neurosignatures that promote a sense of unity and health within the body-self neuromatrix.

The rehabilitation process will initiate, at least, 72 hours after the last sprain. In this situation the tissue inflammation will be reduced and the patients will be able to perform the movements with HD-tDCS.

The rehabilitation process is divided in 3 phases:

1. The first stage is characterized by resistance training and interventions that target both sensory and motor aspects of foot and ankle control. This items coupled with pain reduction are the goal of restoring motion to the ankle progressively during the rehabilitation process. Reducing pain is not only important from the perspective of tissue healing but also for preventing adverse alterations in the neurosignature patterns within the body-self neuromatrix (74).

   Through this lens, joint mobilizations, plantar massage, stretching, and strengthening techniques serve to give inputs related to the local perception of the ankle and foot through articular, cutaneous, and musculotendinous stimulation. Controlled progressive motion passively, actively, and with resistance reduces the local structural and functional impairments(11).

Rehabilitation Goals	Success criteria	Assessment instruments
1-. Increase range of motion (ROM) and strength of muscles around the ankle. 2-. Improve neuromuscular control. 3-. Pain reduction. 4-. Improve self-ability	1.1. Increase ROM 10-15%, in relation with the first session. 1.2. Increase isometric ankle strength 20-25%. 2.1. Reduction in stabilization time. 3.1. Reduction in 2 points in 11 points scale NRS.	1.1. Knee-to-wall exercise. MyROM app(70). 1.2. Ankle isometric force. Strain gage(75). 2.1. Force plate (Bertec FP6090-15, Columbus, OH)(3) 3.1. NRS

Rehabilitation contents	Progression	Example Exercises
1. Joint active mobilization. 2. Joint passive mobilization 3. Isometric strengthening. 4. Early weight bearing. 5. Reaction to stimulus in the foot.	- From internal focus to external focus. - From isometric contractions to excentric and plyometrics. - From predictable to unpredictable environment.	1-. Knee-to Wall 2-. Ankle mobilization in different axis without pain. 3-. Ankle isometric contraction with the resistance of physiotherapist. 4-. Gait mechanics with support in pararell bars. 5-. Touch with the finger one part of the foot and the patient must follow the finger.

Table 2 Therapeutic exercise framework. Stage 1

2. The second stage is characterized by task and environment manipulation for introduce functional movement exercises(11). The patient is unable to perform sport specific abilities with diminished self-efficacy, feeling of pain and avoidance with sport specific activities. Once the ability to balance was learned, it appeared to be retained and the patients were able to progress to more difficult balance challenges. In this way, the error-based progression with the purposeful manipulation of task and environmental constraints in the context of sport-specific activities enhances the perception of mastery of sport-specific demands(11,76).

Rehabilitation Goals	Success criteria	Assessment instruments
1-. Increase range of motion (ROM) and strength of muscles around the ankle. 2-. Improve neuromuscular control. 3-. Pain reduction.	1.1. Increase ROM to 85% of full ROM. 1.2. Increase isometric ankle strength 50-65%. 2.1. Reduction in stabilization time. 3.1. Reduction below 4 in 11 points scale NRS.	1.1. Knee-to-wall exercise. MyROM app(70). 1.2. Ankle isometric force. Strain gage(75). 2.1. Force plate (Bertec FP6090-15, Columbus, OH)(3)

		3.1. NRS
Rehabilitation contents	Progression	Example Exercises
1. Joint active mobilization. 2. Wobble board in one axis 3. Predominantly, Isometric and concentric strengthening. 4. Coordination in coordination scale without high hops. 5. Improve gait mechanics 6. Reaction to stimulus in the foot.	- From internal focus to external focus. - From isometric contractions to excentric and plyometrics. - From predictable to unpredictable environment.	1-. Knee-to Wall 2-.Control wobble board. 3-. Triple flexion exercises like squat (coordination with other joints). 4-. Lateral displacement in coordination scale 5-. Gait mechanics without support. 5-. Touch with the finger one part of the foot and the patient must follow the finger.

Table 3Therapeutic exercise framework. Stage 2

3. The third stage is characterized by the inability to play the sport. Coordination training via purposeful and progressive manipulation of task and environmental constraints affords perceptual tuning of the body-self connection. Skill reacquisition, then, is the optimization of the relationship between perception and action in a system that has been constrained by injury or illness. A patient should be progressed to more complex tasks and unpredictable environments when there is evidence of a shift from a high to a low cognitive load while also maximizing the outcome of the movement goal (11,76).

Rehabilitation Goals	Success criteria	Assessment instruments
1-. Achieve full range of motion (ROM) and strength of muscles around the ankle. 2-. Improve neuromuscular control and coordination in unpredictable context.	1.1. Full ROM. 1.2. Increase isometric ankle strength 90-100%. 2.1. Reduction in stabilization time.	1.1. Knee-to-wall exercise. MyROM app(70). 1.2. Ankle isometric force. Strain gage(75).

3-. Pain reduction.	3.1. Reduction below 2 in 11 points scale NRS.	2.1. Force plate (Bertec FP6090-15, Columbus, OH)(3) 3.1. NRS
Rehabilitation contents	Progression	Example Exercises
1. Joint active mobilization. 2. Wobble board in all axis 3. Multitask exercises with external focus combining all types of contraction and simulation of sport context. 4. Plyometrics. 5. Improve gait mechanics	- From internal focus to external focus. - From isometric contractions to excentric and plyometrics. - From predictable to unpredictable environment.	1-. Knee-to Wall 2-.Control wobble board stand up position. 3-. Reaction to external stimuli and movement in different directions 4-. Jump up the hurdles. 5-. Gait mechanics in fatigue.

Table 4Therapeutic exercise framework. Stage 3

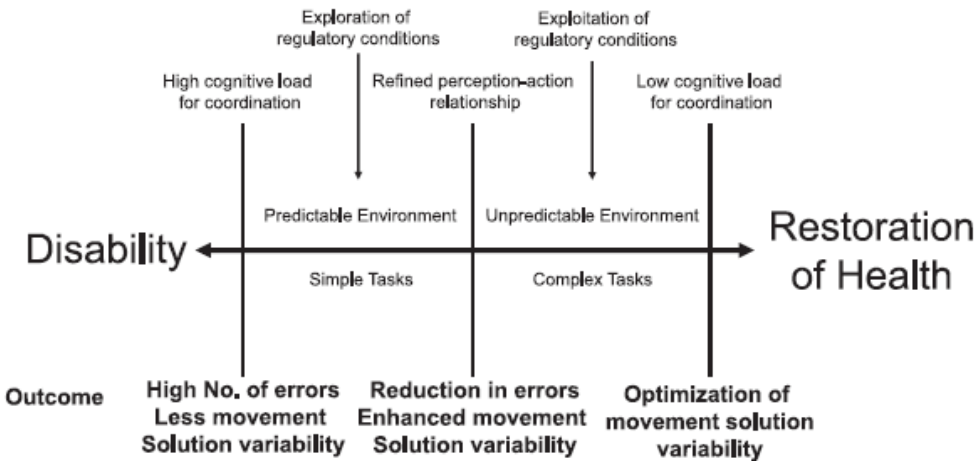

Figure 5 Intervention based framework from Mckeon et al. (11)

Whereas the patients in control group are performing the rehabilitation tasks, sham HD-TDCS will be applicated to them. Concretly, the real and sham HD-TDCS will be applicated when the patients perform knee-to-wall exercise at the start of the session.

Garnett and Ouden (77) recently validated a sham condition for use in HD tDCS: the anodes and cathodes are located in the same position as in the stimulation condition, but the current direction is changed. The current crosses the scalp in a superficial way, creating in the subject a sensation of stimulation effect, but not reaching cortical areas. Subjects were not able then, to distinguish the stimulation from the sham condition. By using the same electrode configuration as in our two active stimulation conditions, but with current flow limited primarily to the scalp through the use of adjacent pairs of electrodes of opposite polarity, we were able to effectively blind our participants to the type of stimulation they received each session(35).

4.11.2. Experimental group

Whereas the therapeutic treatment is applied, the real HD-tDCS is applicated in 4 x 1 ring configuration with a current strength of 2 mA for 10 min (both for anodal or cathodal tDCS) by a battery-driven constant current stimulator (NeuroConn GmbH, Ilmenau, Germany). This type of NIBS is safe, and is possible to applicate when the exercise is carrying out. We decide to applicate in the exercise knee-to wall because is a type of exercise that is in all stages of rehabilitation and show the characteristic that in this motion pattern the muscles try to stabilize the ankle (35,78).

Measurements based in Villamar et al. (41).
To localize the “hotspot” in the M1. First, localize the vertex (Cz). 1. In order to do this, measure the distance from the nasion to the inion and divide the distance by half. The nasion is the spot at the junction of the forehead and the nasal bones, and the inion is the most prominent point of the occipital bone. Mark the spot as a line.
2. Secondly, measure the distance between the left and right pre-auricular points (*i.e.* the area anterior to the tragus). Divide this distance by half, and mark the spot with a line. Now connect both lines to create a cross. The point at which both lines intersect corresponds to Cz.

3. In order to stimulate over the primary motor cortex (M1), calculate 20% of the distance from Cz to the left or right pre-auricular point, beginning the measurement at Cz.
4. Afterwards, we put the modular EEG recording cap keeping the M1 mark in sight, To keep the M1 cross mark on the scalp in sight, one can move the hair around before placing the HD casing over it. Ensure that the cap fits snugly but comfortably, and adjust the position of the four return plastic casings. we positioned the return electrodes in a radius of 3.5 cm from M1. Their locations corresponded roughly to FC3, C1,CP3 and C5, use a measuring tape to confirm that the inter-electrode distance is correct.

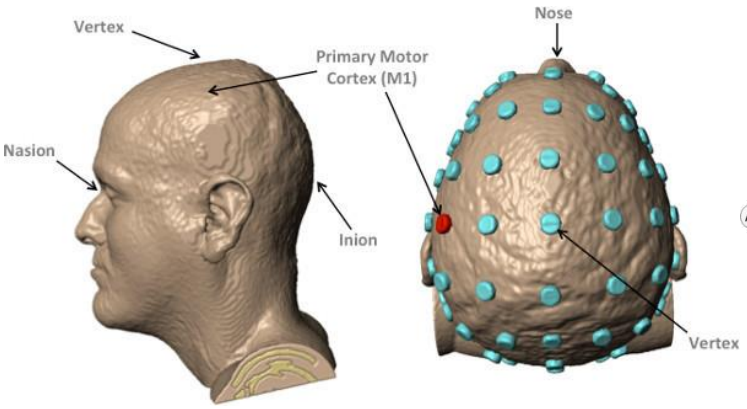

Figure 7 Measurements illustration to 4x1 ring HD-tDCS, Villamar et al.(41)

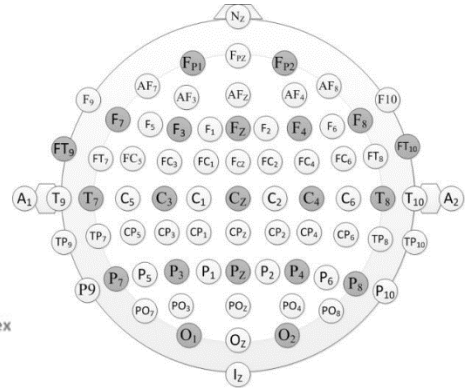

Figure 6 Disposition 4X1 ring of HD-tDCS at FC3,C1,CP3 and C5 (83)

4.11.3. Electrode positioning and device setup (41)
Separate the hair through the opening in the plastic casing until the scalp is exposed. Repeat under each casing.
Introduce approximately 1.5 ml of electrically conductive gel through the opening of each plastic casing, beginning at the scalp surface. Application of the gel can be achieved using a plastic syringe. Carefully avoid spreading gel beyond the circumference of the plastic casing, as this may lead to shunting of electrical current and inadequate current flow.
Next, with its rough surface facing down and the smooth rounded surface facing up, position one Ag/AgCl sintered ring electrode in each HD plastic casing. Add some more gel to cover the electrode, and then use the caps provided with the HD plastic casings to lock the electrodes in place.

This cap will keep the electrode in place throughout the stimulation. Rotate the cap to lock it in position.
Connect the rounded end of the output cable to the 4x1 Adapter output port. Use the input cable to connect the 4x1 Multichannel Stimulation Adapter to the conventional tDCS device. When the connections are ready, turn on both devices.
Do not activate the conventional tDCS device while the 4x1 Multichannel Stimulation Adapter is in "Scan" (impedance check) mode, as stimulation will not be delivered to the subject. Initiate the HD-tDCS session by pressing the "Start" button of the conventional tDCS device. The "Start" light will flash as DC intensity is ramped up and then light continuously when target current is reached. The timer will then show the remaining time and the "True Current" indicator will show the current intensity delivered to the center electrode and the four return electrodes combined

Table 6 Electrode positioning and device setup

Real HD-tDCS: 4 × 1 HD tDCS ring configuration (compounded by four cathodes and one central anode) located at primary motor cortex (M1). The cathodes are at 3.5 cm distance from the anode which were connected to a four-to-one wire adaptor for the DC stimulator (78). Altogether 5 sintered Ag/AgCl ring electrodes (outer radius: 12 mm, inner radius: 6 mm) were stabilized with plastic holders filled with EEG conducting gel (78)(H þ H Medical Devices, Germany and with gel-skin contact area w25 2.5 mm2). HD-tDCS was administered with a current strength of 2 mA for 15 min (79,80) (both for anodal or cathodal tDCS) Electrodes will be connected to a 4 × 1 HD-tDCS Adaptor and a SMARTscan Stimulator (Soterix).

5. Calendar.

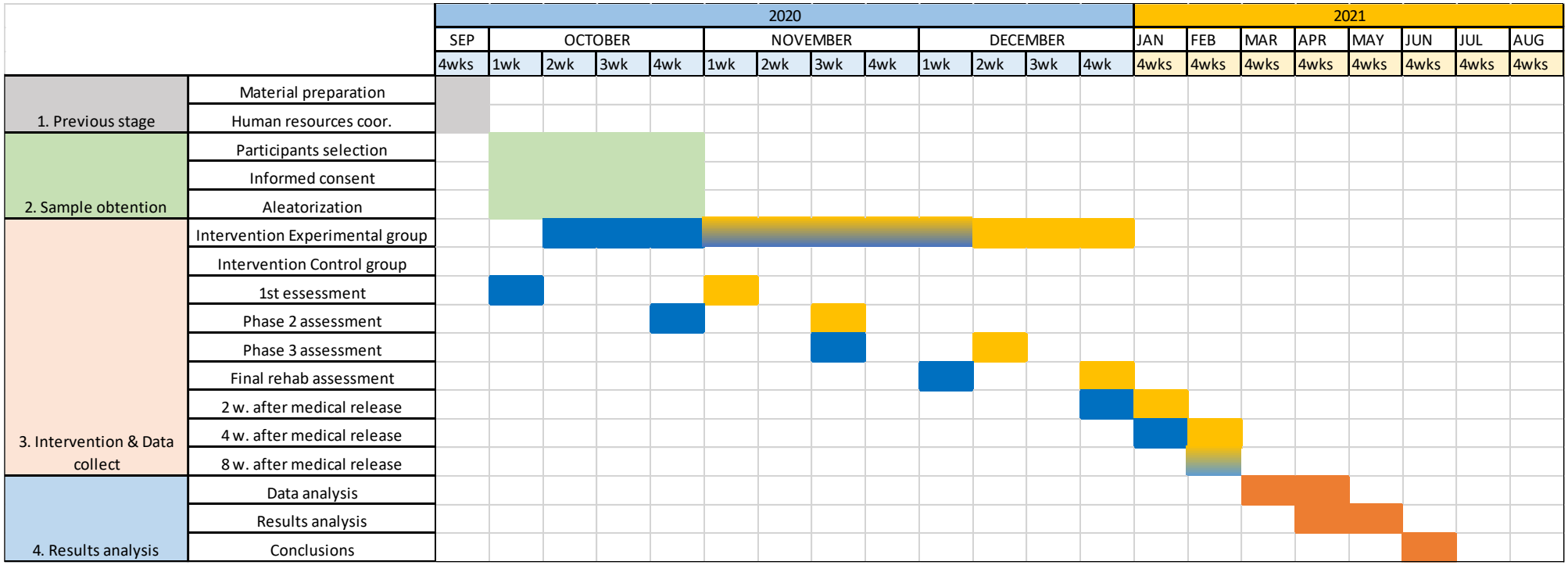

Table 7 Study calendar

The stage 1 and 4 is common for all subjects. Nevertheless, the sample obtention and the intervention &data collection stage is design specifically for each study participant. The participants will be recluted since 1st until 31st of October and 72 hours after the diagnostic each participant will start the rehab process.

I have reflect in blue colour the participants that are diagnosed the first week of October, whereas in yellow are the participants that are diagnosed the last week of October. Between this two examples will be all the study subjects.

6. Limitations and biases.

The study has some limitations and biases. First, the ramdomness is not use to choose the sample. This is not possible owing to selection criteria and the time that we are able to select study patients.

The sample elected could affect to the intern validity because the people diagnosed in one month with CAI in the HPI and HGC is limited, for this reason we send e-mail for each sport federation that have participants in Castellón province. Also, people that came previously to the Hospital with CAI diagnostic could be included to the study if they do not start any type of rehabilitation, obviously , all of this participants must satisfy the elegibility criteria.

Other limitation is that could exist the possibility for small modifications in the exercises prescribed for primary care physiotherapists. In this case, there may be little modifications that could affect the rehabilitation result, however, we assume this limitation because variability movements and exercises are important for each individual and at the end of the study will have treated following action framework explained before in the intervention plan. For reduce this limitation, the primary care physiotherapist will be trained for avoid significant differents between treatments even if they follow the action framework.

Experimenter bias is reduced with the double (Physiotherapists and study participants) blinded design. However, the statistic will know at what group pertain the patients.

Secondly, could be selection bias due to the participant losses between the data collect. Because when the study participants have the medical release they must come to the hospital 2, 4 and 8 weeks after to do the assessment of dependent variables.

Generalizability of findings is not assured even if internal validity of a research study is addressed effectively through design. Strict controls to ensure internal validity can compromise generalizability.Nevertheless, due to other chronic injuries have changes at neuroplastic level (24) the combination of therapeutic exercise and HD-tDCS could be applied, because HD-tDCS have demostrated the effectivity, safety and the easy applicability in many other situations like Parkinson desease or strokes(35).

In other hand, the exclusion criteria limit the external validity being that only adults that practice sport are accepted in the study (see exclusion variables at 4.4).

7. Ethic Problems.

The key principles of respect for persons, beneficence and justice therefore aim at safeguarding the rights of the research subjects. Researchers must continue to uphold these moral principles during the conduct of research in order to avoid exploiting research subjects. While adding to the body of knowledge through research, it is absolutely necessary to be mindful of the process and treat the research subjects with all the dignity they deserve (81).

For this reason, the subjects should read and sign informed consent (Annex 3), know their rights and being conscious of the study process, inform about conflict interest and guarantee the data confidentiality. The experimental protocol will be approved by Clinical Research Ethics Committee following Helsinki Declaration (82). In this way, the study must comply with two laws "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales" cita and "Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".

The participants will be free for sign or not the informed consent, only they that sign will be elected to the assessment. Coupled with informed consent there will be information sheet that explain the investigation procedure (Objectives, methodology, risks, timeline and data management) (Annex 4).

8. Study organization.

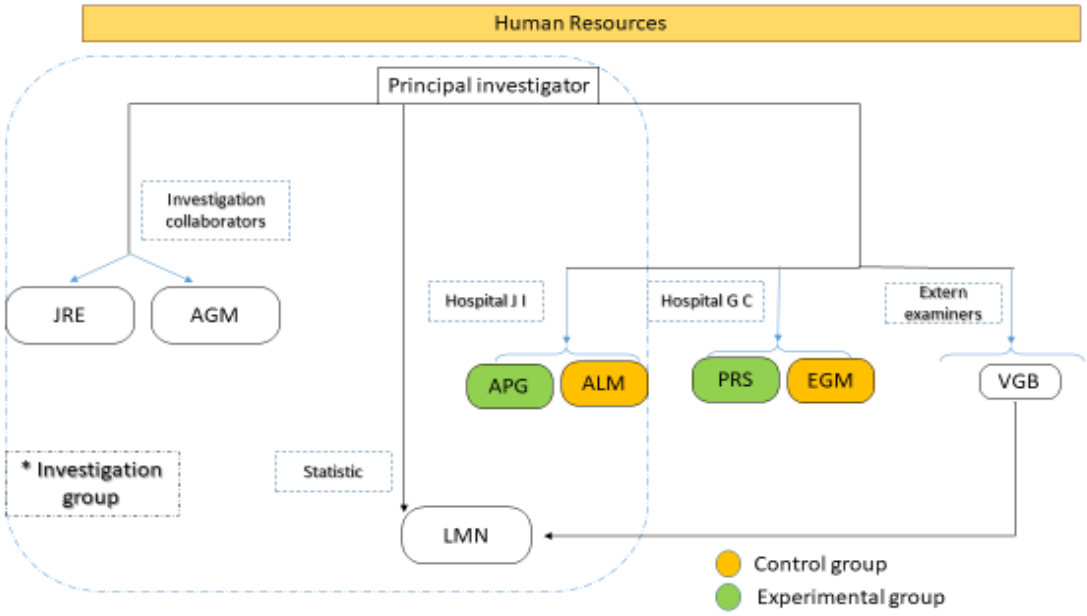

Figure 8 Human Resources that participate in the study

Study preparation (September 2020):

Before the study start, principal investigator contact with the reference Hospital in Castelló to explain the investigation project and proposed a collaboration between the investigation group and the Hospital to do the study in their facilities. In addition, the investigation group are searching information to redact the study theoretical framework.

Whereas, investigation collaborators send e-mails to the sport federations that have place in Castelló to attract participants with CAI.

In other part, extern examiners are preparing and have formation to have good manoeuvrability with HD-TDCS device.

Participants selection (October 2020):

The principal investigator is responsible for evaluate the exclusion and inclusion criteria for the study, whereas the investigation collaborators give information about the study to the CAI patients. Then, if the patients accept, they sign the informed consent and complete the questionnaire.

In this moment, the principal investigator ring the participants to accord one day to do the assessment with the extern examiners. This process will be done staggered, only one participant at the same time with the examiner. This examination process will be done at least 72 hours after the last sprain or ankle giving away symptom.

Study initiation:

Following the assessment of dependent variables done by extern examiners the statistic will make the participants randomization granting one ordinal number to each participant. When this is done, the primary care physiotherapist will have a sheet with the diary schedule and each patient will come to the Hospital at the hour that is predicted. At this time, neither the patients and primary care physiotherapist know if they are treating the control group or the experimental group, they only follow the rehabilitation CAI framework and the guidelines to provide HD-TDCS. Previously, the principal investigator will programme the HD-tDCS stimulator with HD-Explore™ software to provide real or shame stimulation, the primary care physiotherapist will click the patient number and the program automatically knows what type of stimulation have to provide. This work is done with the statistic and ensure that both the patients and physiotherapist are blinded.

While the patients are working in the rehabilitation following the physiotherapist instructions these physiotherapist are responsible to determine when the study subjects are prepared to pass

into the next stage. In this way, the primary care physiotherapist will communicate with extern examiners and fixed one day to the dependent variables assessment.

Data analysis:

When the rehabilitation process is finished the statistic will analyse all the data to extract results and conclusions.

Material Resources:

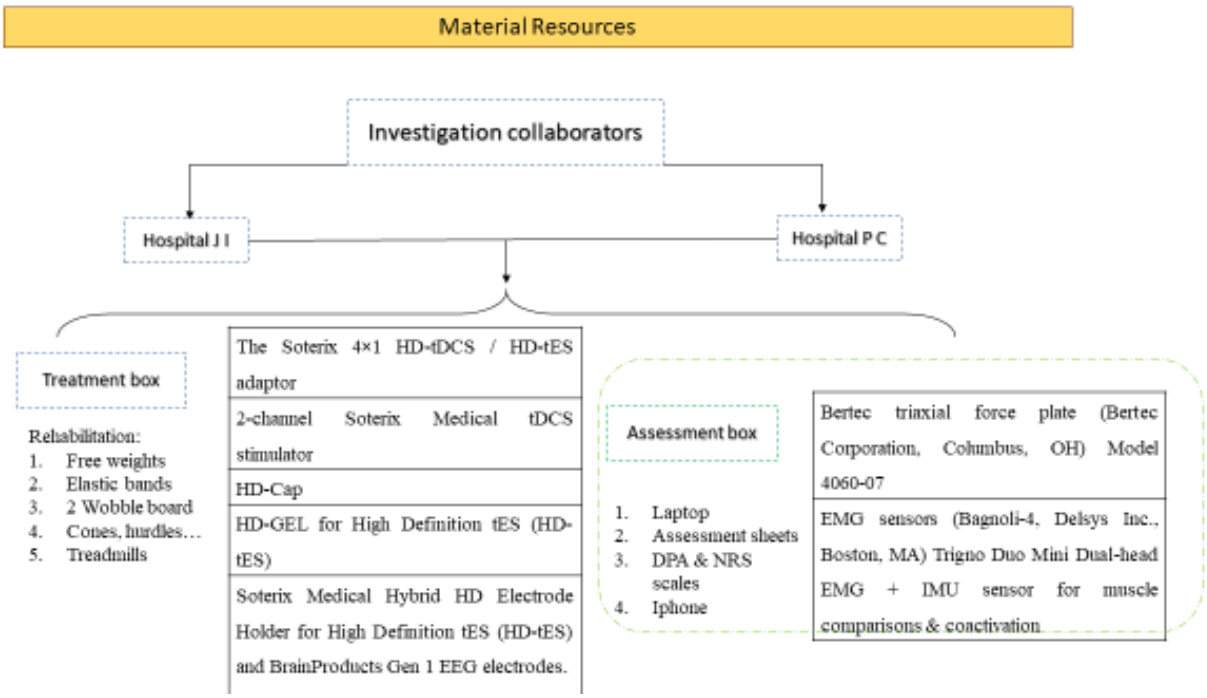

Figure 9 Material resources for the study

The investigation collaborators will be responsible to locate the material in the treatment box and the assessment box. This material will be saved in one Hospital JI room, except the Iphone and the laptop that investigation collaborators are the owners.

The principal investigator will lead an agreement with the Hospitals to use their rehabilitation material for our study. In addition, the principal investigator is in contact constant with Soterix enterprise if there are any problem with the HD-TDCS devices or need more material for the study development.

9. Budget:

Items	Number	Price
The Soterix 4×1 HD-tDCS / HD-tES adaptor	2	1100€
2-channel Soterix Medical tDCS stimulator	2	2300€
HD-Cap	4	60€
HD-GEL for High Definition tES (HD-tES)	20	200€
Soterix Medical Hybrid HD Electrode Holder for High Definition tES (HD-tES) and BrainProducts Gen 1 EEG electrodes.	20	500€
Free weights	Hospital material	Accordance with Hospital
Wobble boards	Hospital material	Accordance with Hospital
Elastic bands	Hospital material	Accordance with Hospital
Cones and hurdles (coordination items)	Hospital material	Accordance with Hospital
Treadmills	Hospital material	Accordance with Hospital
Laptop	Investigation group material	Own laptop
Bertec triaxial force plate (Bertec Corporation, Columbus, OH) Model 4060-07	1	3500€
EMG sensors (Bagnoli-4, Delsys Inc., Boston, MA) Trigno Duo Mini Dual-head EMG + IMU sensor for muscle comparisons & coactivation	1	650€
LabView Software	1	150€
HD-Explore™ software	1	200€
ROM Iphone app	1	9.99€

SPSS Statistics	1	96€
Salaries		
Extern examinators	2	3000€
Primary care physiotherapists	4	Accordance with Hospital
		11765.99 €

Table 8 Study budget

For the study funding we will apply for research fellowship and different financial aids:

- "Fundacion Española del dolor"(FED) grants between 1500€ to 3000€. With this initiative, the FED seeks to promote the launch of research projects and motivate the start of research vocations of the SED members in the area of pain or contribute to the support of researchers already initiated.
- Research grants from the " Col·legi de Fisioterapeutes de Catalunya" for projects with a maximum duration of 2 years.
- Research grant from " Universitat de Lleida" (Beques d'introducció a la recerca)
- Research grants "Ignacio H. de Larramendi" from "Fundación Mapfre" with maximum import of 30.000€ and duration of 1 year.

Also, we have agreement with the Hospitals that participate in the study for use their facilities and material.

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11. Annex

Annex 1.

Screening at "Hospital Jaume I de Castelló" or " Hospital General Universitari de Castelló" following the selection criteria of the International Ankle Consortium.

EXCLUSION CRITERIA
A history **of previous surgeries** to the musculoskeletal structures (ie, bones, joint structures, nerves) in either limb of the lower extremity
A history of a **fracture in either limb** of the lower extremity requiring realignment
Acute injury to musculoskeletal structures of other joints of the lower extremity **in the previous 3 months,** which impacted joint integrity and function (ie, sprains, fractures) resulting in at least 1 interrupted day of desired physical activity

INCLUSION CRITERIA
A history of at least **1 significant ankle sprain**. The last 3 months before the screening.
A history of the previously injured ankle joint "**giving way**" and/or recurrent sprain and/or "feelings of instability."
Specifically, **self-reported ankle instability** should be confirmed with a validated ankle instability specific questionnaire. Identification of Functional Ankle Instability **(IdFAI)**: > 11
A general self-reported foot and ankle function questionnaire. Foot and Ankle Ability Measure (**FAAM**): ADL scale < 90%, Sport scale < 80%

Gribble PA, Delahunt E, Fong DT, Hertel J, Hiller CE, Thomas W, et al. Selection Criteria for Patients With Chronic Ankle Instability in Controlled Research: A Position Statement of the International Ankle Consortium. J Athl Train. 2014;49(1):121–7.

Annex 2. Disablement in the physical Activity Scale

Disablement in the Physically Active Scale©

Instructions: Please answer **each statement** with one response by shading the square that most closely describes your problem(s) within the past **24 hours**. Each problem has possbile descriptors under each. Not all descriptors may apply to you but are given as common examples.

0- No problem
1- I have the problem(s), but it does not affect me
2- The problem(s) slightly affects me
3- The problem(s) moderately affects me
4- The problem(s) severely affects me

DPA-Physical Summary Component	**No Problem** 0	**Does not affect** 1	**Slight** 2	**Moderate** 3	**Severe** 4
Pain- "Do I have **pain**?"	☐	☐	☐	☐	☐
Motion- "Do I have impaired **motion**?" Ex. Decreased range/ease of motion, flexibility, and/or increased stiffness	☐	☐	☐	☐	☐
Muscular Functioning- "Do I have impaired **muscle function**?" Ex. Decreased strength, power, endurance, and/or increased fatigue	☐	☐	☐	☐	☐
Stability- "Do I have impaired **stability**?" Ex. The injured area feels loose, gives out, or gives way	☐	☐	☐	☐	☐
Changing Directions- "Do I have difficulty with **changing directions** in activity?" Ex. Twisting, turning, starting/stopping, cutting, pivoting	☐	☐	☐	☐	☐
Daily Actions- "Do I have difficulty with **daily actions** that I would normally do?" Ex. Walking, squatting, getting up, lifting, carrying, bending over, reaching, and going up/down stairs	☐	☐	☐	☐	☐
Maintaing Positions- "Do I have difficulty **maintaining the same position** for a long period of time?" Ex. Standing, sitting, keeping the arm overhead, or sleeping	☐	☐	☐	☐	☐
Skill Performance- "Do I have difficulties with **performing skills** that are required for physical activity?"					
1) Ex. Running, jumping, kicking, throwing & catching	☐	☐	☐	☐	☐
2) Ex. Coordination, agility, precision & balance	☐	☐	☐	☐	☐
Overall Fitness- "Do I have difficulty maintaining my **fitness** level?" Ex. Conditioning, weight lifting & cardiovascular endurance	☐	☐	☐	☐	☐
Participation in Activites- "Do I have difficulty with **participating in activities**?"					
1) Ex. Particpating in leisure activities, hobbies, and games	☐	☐	☐	☐	☐
2) Ex. Participating in my sport(s) of preference	☐	☐	☐	☐	☐

DPA-Physical Score = ____/ 48

DPA-Mental Summary Component					
Well-Being- "Do I have difficulties with the following…?"	0	1	2	3	4
1) Increased uncertainty, stress, pressure, and/or anxiety	☐	☐	☐	☐	☐
2) Altered relationships with team, friends, and/or colleagues	☐	☐	☐	☐	☐
3) Decreased overall energy	☐	☐	☐	☐	☐
4) Changes in my mood and/or increased frustration	☐	☐	☐	☐	☐

DPA-Mental Score = ____/ 16

DPA-Total Score = ____/ 64

(DPA-Mental + DPA-Physical)

Fig. 2 Physical and mental summary components of the Disablement in the Physically Active scale. Adapted with permission from Vela and Denegar [4]

Annex 3. Informed consent

ACTA CONSENTIMIENTO INFORMADO

Yo, (nombre y apellidos) ……..……
con DNI……

Declaro haber sido informado/a de los objetivos, procedimientos del estudio y del tipo de participación.

Declaro haber sido informado/a que mi participación no involucra ningún daño o peligro para su salud física o mental, que es voluntaria y que puedo negarme a participar o dejar de participar en cualquier momento sin dar explicaciones o recibir sanción alguna.

Declaro saber que la información entregada será confidencial y anónima. Entiendo que la información será analizada por los investigadores en forma grupal. La información que se obtenga será guardada por el investigador responsable y será utilizada sólo para este estudio. Por otra parte, he sido informado y entiendo que los datos obtenidos en el estudio pueden ser publicados o difundidos con fines científicos y/o educativos.

Este documento se firma en dos ejemplares, quedando uno en poder de cada una de las partes.

Acepto participar voluntaria y anónimamente en el Protocolo de Investigación" Análisis prospectivo de los efectos de la neuroestimulación no invasiva (HD-TDCS) combinado con ejercicio terapéutico en pacientes adultos con inestabilidad crónica de tobillo, comparada con ejercicio terapéutico y HD-TDCS placebo. Estudio controlado aleatorizado doble ciego y prospectivo" después de leer y comprender la información expuesta por el responsable del estudio.

Nombre Participante	Firma	Fecha

Nombre Investigador Responsable	Firma	Fecha

Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales" cita and "Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".

Annex 4. Study Information.

Hoja de información al paciente

1. Introducción:

Nos dirigimos a usted para informar-le sobre los aspectos más relevantes del estudio y proporcionarle toda la información necesaria para determinar si quiere participar o no en el estudio. De todas maneras, si necesita cualquier aclaración puede dirigirse al investigador principal vía e-mail y resolver todas sus dudas previas a su decisión.

2. Objetivos del estudio.

El objetivo principal del estudio es:

- Analizar la efectividad de la estimulación corriente directa transcraneal de alta definición (HD-tDCS) combinada con ejercicio terapéutico en pacientes adultos deportistas con inestabilidad crónica de tobillo, comparado con ejercicio terapéutico y HD-tDCS placebo.

Como objetivos secundarios del estudio:

- Evaluar en pacientes adultos deportistas con inestabilidad crónica del tobillo la efectividad de HD-tDCS combinado con ejercicio terapéutico en comparación con el ejercicio terapéutico basado en evidencia para mejorar la calidad de vida relacionada con la salud.

- Evaluar la evolución del rango de movimiento del tobillo en el grupo experimental durante el tratamiento combinado de HD-tDCS y ejercicio terapéutico.

- Evaluar la evolución de la fuerza de los peroneos corto y largo en el grupo experimental durante el tratamiento combinado de HD-tDCS y ejercicio terapéutico.
- Comparar entre el grupo experimental y el grupo control la función y el dolor en pacientes con IAC.

3. Metodología.

Diseño de investigación: Ensayo prospectivo, doble ciego, aleatorizado y controlado (ECA) diseñado en adultos atléticos con ICA.

Muestra: La muestra estará formada por adultos deportistas diagnosticados con ICA siguiendo los criterios de "International Ankle Consortium".

Aleatorización: Los sujetos se dividirán en dos grupos mediante una aleatorización realizada con software libre, se realizará una aleatorización simple. Además, los pacientes y el fisioterapeuta estarán cegados y no sabrán en qué grupo se encuentran.

4. Descripción del tratamiento.

Intervención*:* Habrá dos grupos, el grupo experimental tratado con ejercicio terapéutico y HD-tDCS real, mientras que el grupo control será tratado con ejercicio terapéutico y HD-tDCS placebo. La intervención es de 8 semanas, luego los pacientes serán seguidos durante 8 semanas más. El tratamiento se divide en 3 etapas en las que los pacientes superarán en proporción con su progresión.

Medidas: Habrá 7 evaluaciones para los pacientes del estudio. Una antes del inicio de la rehabilitación, dos durante la intervención, otra cuando la rehabilitación ha finalizado y tres más a las 2, 4 y 8 semanas, respectivamente, desde el final de la rehabilitación. Las variables que se evalúan son dolor (escala NRS), control motor (Jump test), calidad de vida relacionada con la salud (escala DPA) y ROM (My Rom app).

5. Beneficios y riesgos.

Con este estudio pretendemos mejorar la salud de los pacientes con los métodos y procedimientos más avanzados que disponemos en el Hospital. De esta forma, queremos que los síntomas y signos de la inestabilidad de tobillo se vean reducidos con una intervención de 8 semanas, además pretendemos que estos efectos perduren en el tiempo.

Se ha reportado la seguridad y fiabilidad del tratamiento que será utilizado. Por tanto, no existen riesgos potenciales que puedan afectar a su salud.

6. Acontecimientos adversos.

Ante acontecimientos adversos durante el estudio, el investigador principal se pondrá en contacto con usted y se determinará la mejor solución para ambas partes. Si estos acontecimientos impiden seguir el tratamiento proporcionado a los pacientes del estudio, otros tratamientos que se ajusten a las circunstancias dadas serán proporcionados.

7. Tratamientos alternativos.

En el caso que usted NO quiera participar en el estudio, el personal sanitario del Hospital le ofrecerá la posibilidad de seguir el tratamiento terapéutico convencional que se sigue con todos los pacientes que muestran inestabilidad crónica de tobillo.

8. Voluntariedad y posibilidad de retirada.

La participación en este estudio es totalmente voluntaria y en todo momento podrá decidir cesar la participación en el estudio, sin que ello tenga consecuencias de ningún tipo.

9. Confidencialidad

La toma de datos y el tratamiento de los datos será ajustada a la "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales" cita and "Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".

El acceso a su información personal quedará restringido a aquellos que pertenecen al grupo de Investigación que lleva a cabo este estudio y a aquellas personas involucradas en el tratamiento de los mismos.

Por otra parte, si por fines científicos se comparten datos con otros grupos de investigación sólo se compartirán datos que no se puedan asociar a su persona.

10. Compensación económica.

Este estudio está financiado con becas y ayudas para la investigación de distinta índole, además existe un acuerdo con los Hospitales en los que se realizará el tratamiento. Por tanto, usted no tendrá ningún gasto por el tratamiento que recibirá, a su vez, tampoco recibirá compensación económica por la participación en dicho estudio.

• Investigador responsable

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Castellón, de del 202 Firmado